Great Neglected Diseases Network

- Started by the Rockefeller Foundation in 1977
- First and only director Kenneth Warren
- Networks of 14 research units across the world (US, UK, Egypt, Australia, Israel, Sweden, Mexico, Brazil, Thailand)
  - Multidisciplinary
  - Emphasis on research - immunology, biochemistry, molecular biology, genetics
  - Disease focus – parasitic infections including malaria
- **Lasted only 8 years**
  - But spawned the careers of a generation of parasite-oriented scientists

The Millenium Development Goals

2000-2015 MDGs

1. Eradicate extreme poverty and hunger
2. Achieve universal primary education
3. Promote gender equality and empower women
4. Reduce child mortality
5. Improve maternal health
6. Combat HIV/AIDS, malaria and other diseases
7. Ensure environmental sustainability
8. Develop a global partnership for development

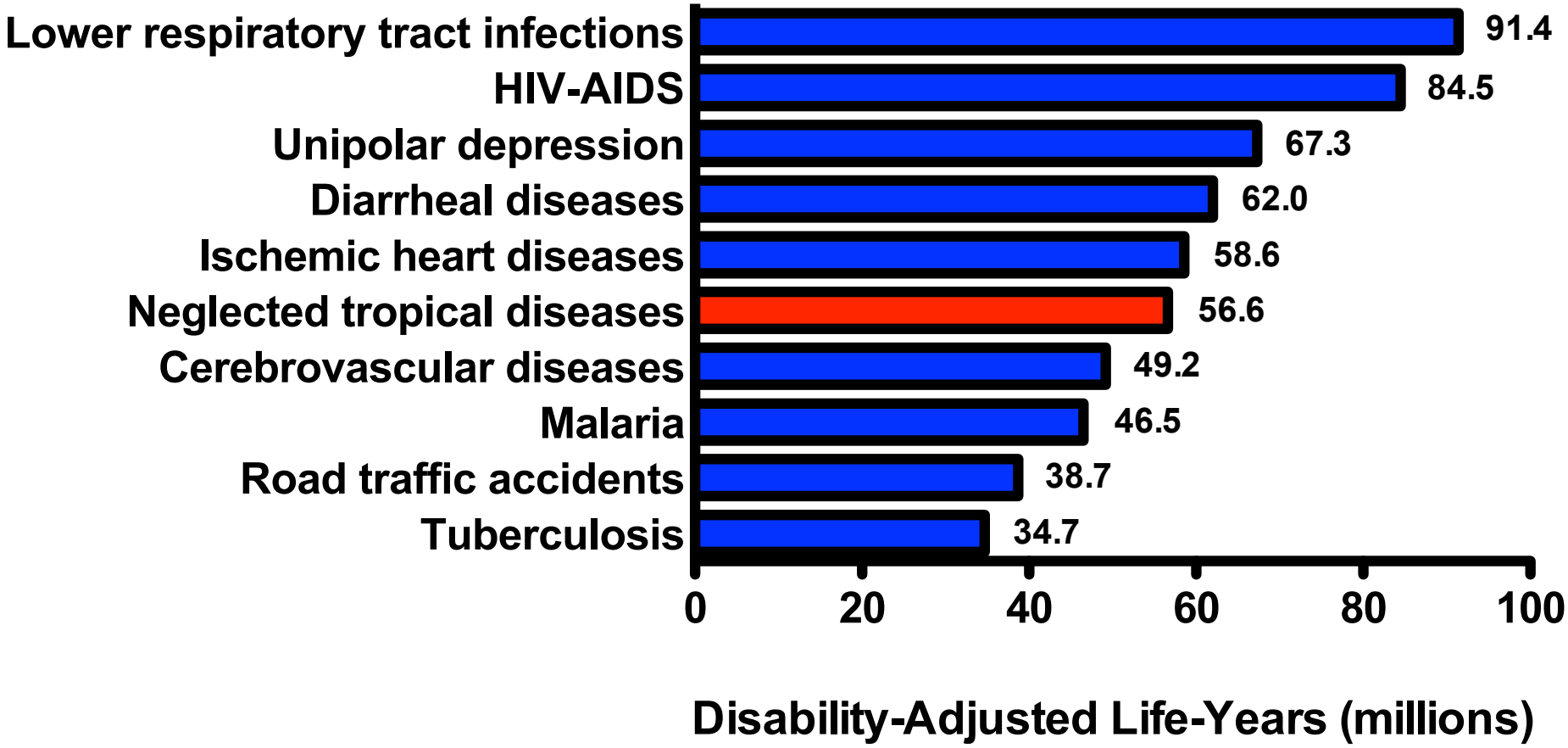
From GNDs to Neglected Tropical Diseases (NTDs)

- Attributed to and popularized by
  - Peter Hotez
  - David Molyneux
  - Alan Fenwick
- Grew out of frustration from the use of the term "Other Diseases" in MDG #6 as it
  - created a two-tier system (HIV, malaria vs everything else)
  - made public advocacy for these "other diseases" impossible
  - left out these "other diseases" in most discussions on global health
- NTD "marketing" has driven funding worldwide

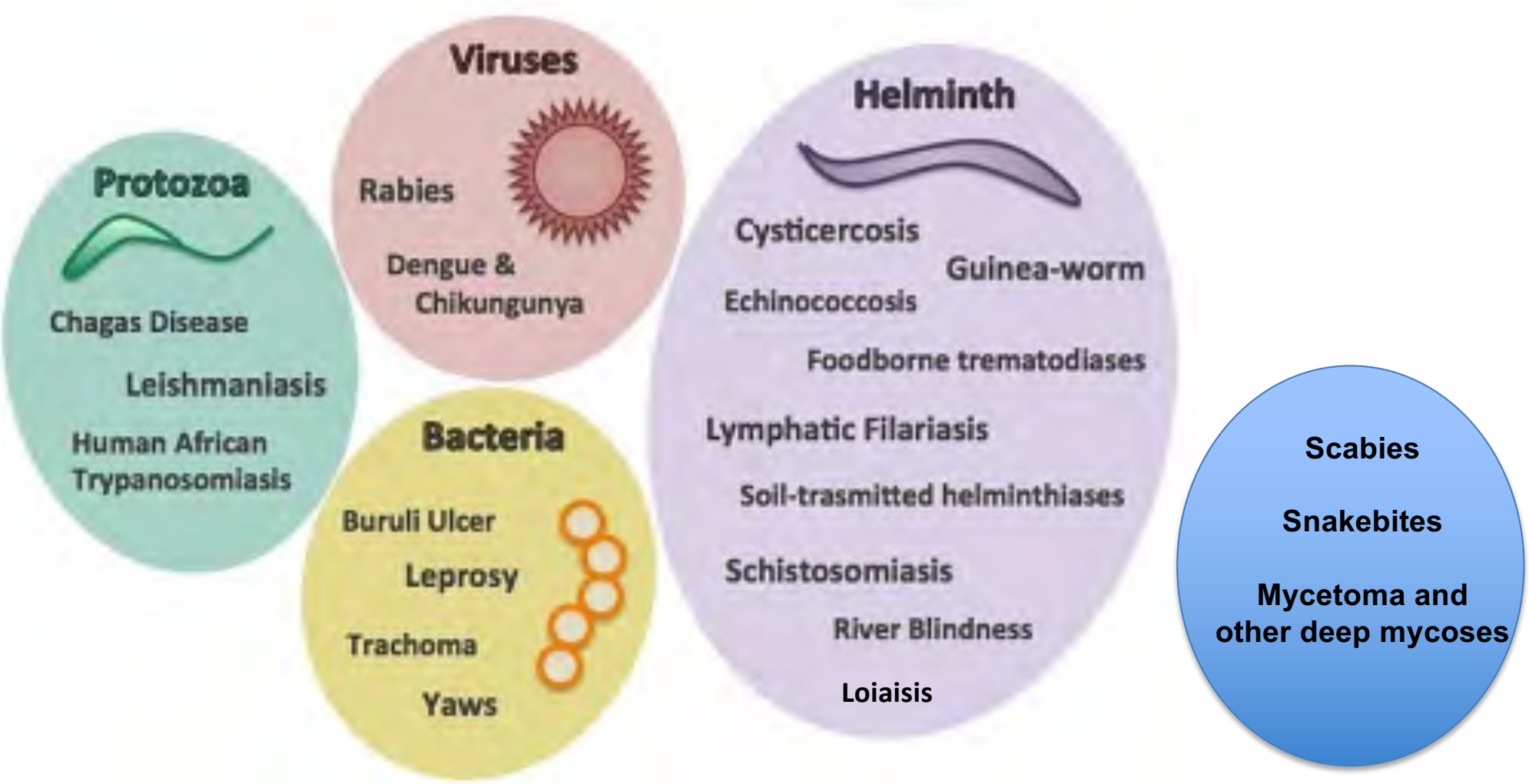
The Neglected Tropical Diseases (NTDs)

- The most prevalent infections of poor people
  - Up to half of the 2.7 billion people who live on less than $2 per day
- Non-emerging ancient conditions
- Indigenous populations
- Chronic disabling conditions
  - Growth delays
  - Blindness
  - Disfigurement
  - Stigma
- Poverty promoting conditions
  - Child development and education
  - Pregnancy outcome
  - Productive capacity

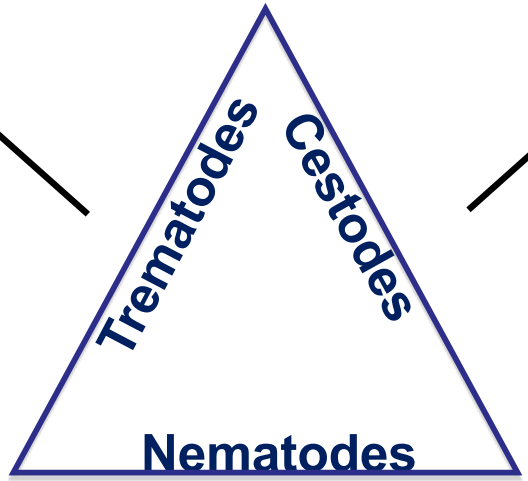
The 10 Leading Causes of Life-Years Lost to Disability and Premature Death



The Neglected Tropical Diseases



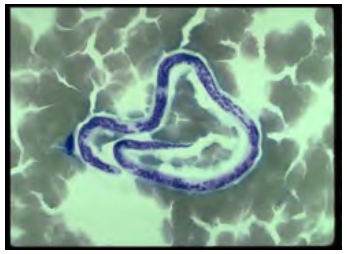
Common Human Helminth Infections



Schistosoma mansoni
>200 million infected

Echinococcus, Taenia spp
>100 million infected

Brugia malayi
Onchocerca volvulus
Wuchereria bancrofti
157 million infected

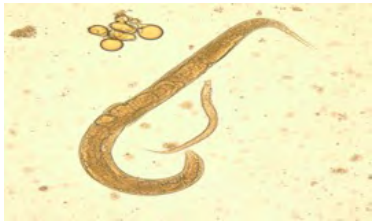


Ancylostoma duodenale
Nector americanus
576 million infected

Ascaris lumbricoides
>1 billion infected

Trichinella spiralis
Trichuris trichiura
600 million infected

Strongyloides stercoralis
50-100 million infected



Babu and Nutman, Clin Immunol, 2017

Filarial Infections of Humans

Infection	Disease	Number infected	Wolbachia
Wuchereria bancrofti	Lymphatic Filariasis	120 million	Yes
Brugia spp.	Lymphatic Filariasis	10 million	Yes
Onchocerca volvulus	Onchocerciasis	29 million	Yes
Loa loa	Loiasis	13 million	No
Mansonella ozzardi	Mansonellosis	?	Yes
Mansonella perstans	Perstans Filariasis	~90 million	Yes
Mansonella streptocerca	Streptocerciasis	?	?

Collectively 2nd leading cause of disability worldwide (>1.2 million DALYs lost)

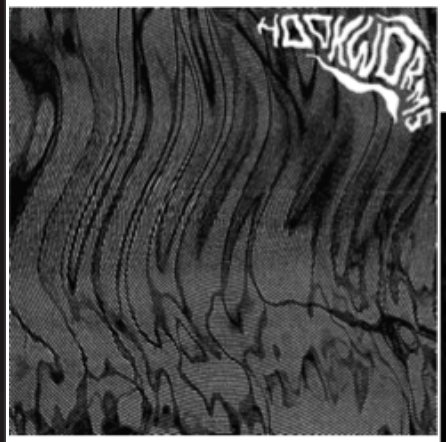

FILARIASIS


RIVER BLINDNESS


Staden Rock'n Roll
Spåren i snön
LOA BAND
musik


THE SHINS


KATAXU
NECATOR


HOOKWORMS


ABARIS
ABARIS

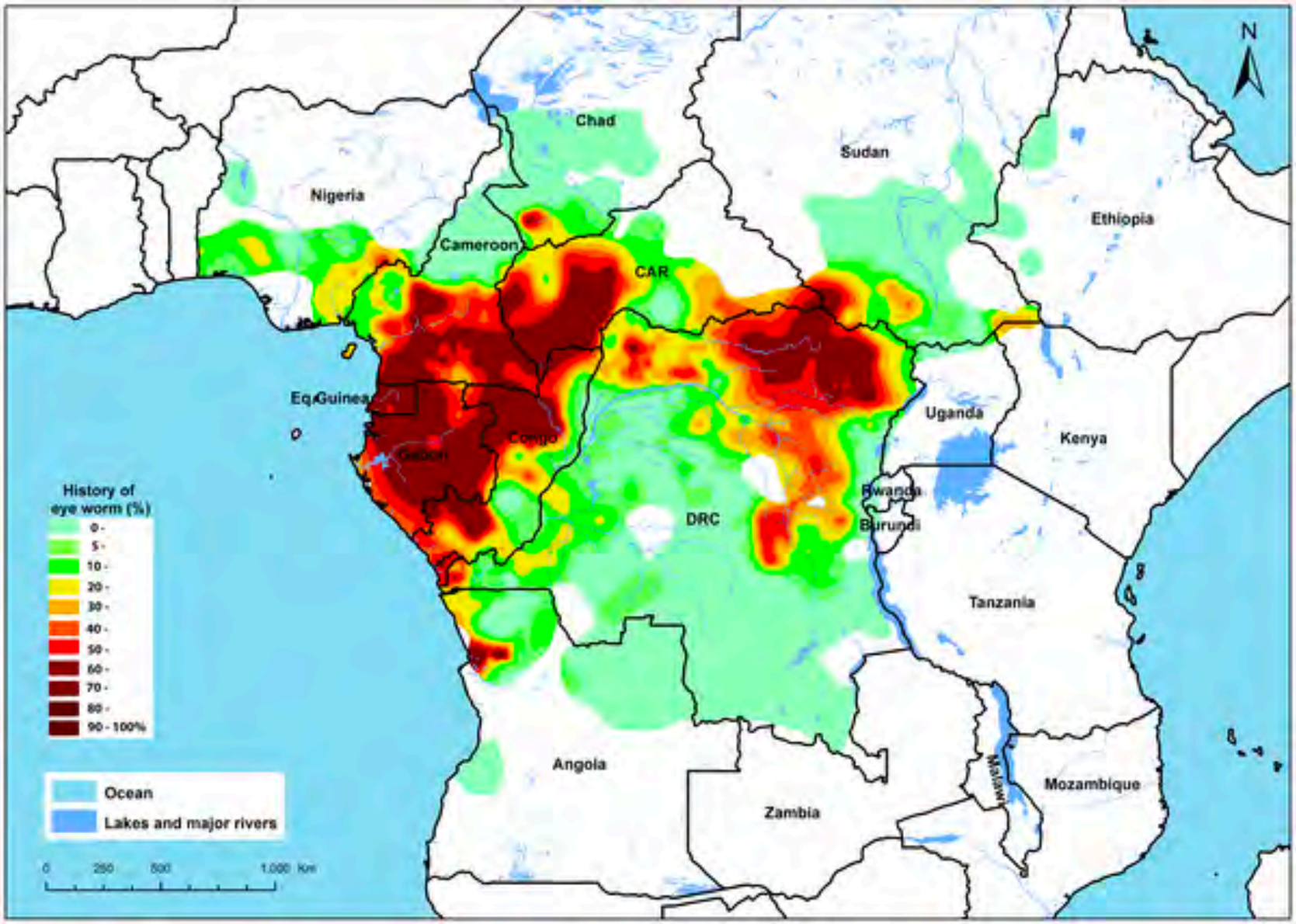

HAIL THE SUN
ELEPHANTITIS


NECATOR

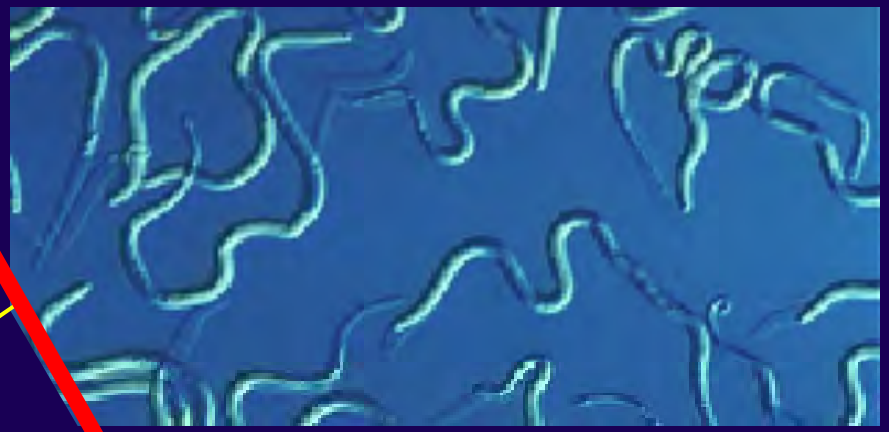
Loiasis

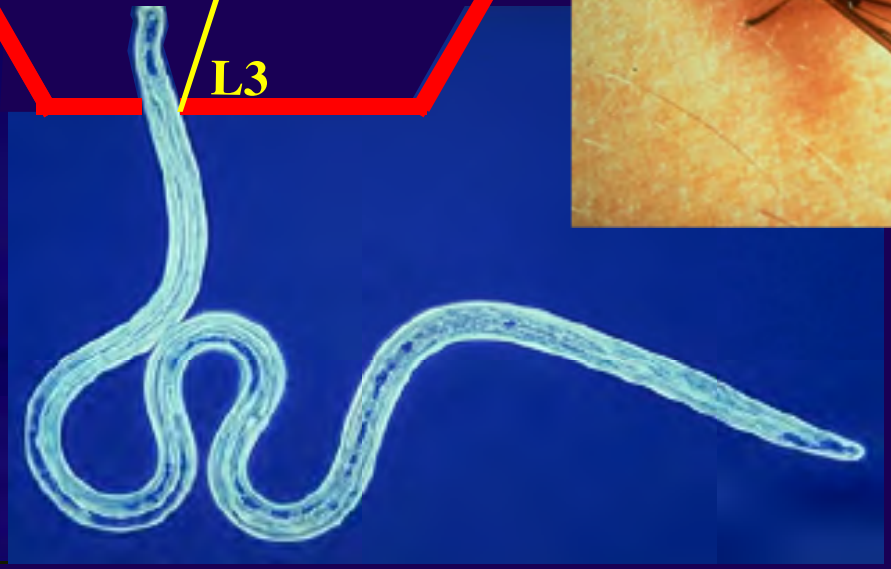
- Ogranism-*Loa loa*
- Vector - Chrysops spp. (deerfly)
- Microfilariae: Blood-borne
- Adult worms: subcutaneous
- Prevalence - 13 million
- Geographic Distribution - West and Central Africa
- Host range - Human

Geographic distribution of *Loa loa* infection



Lifecycle of *Loa loa*

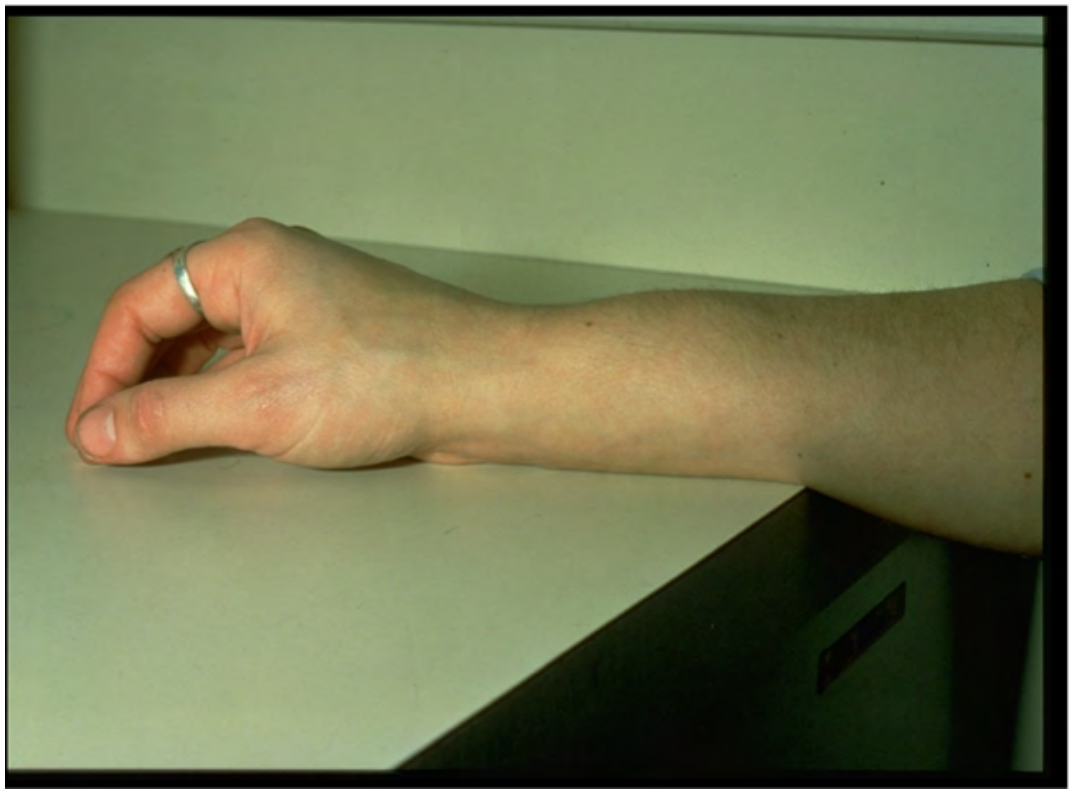




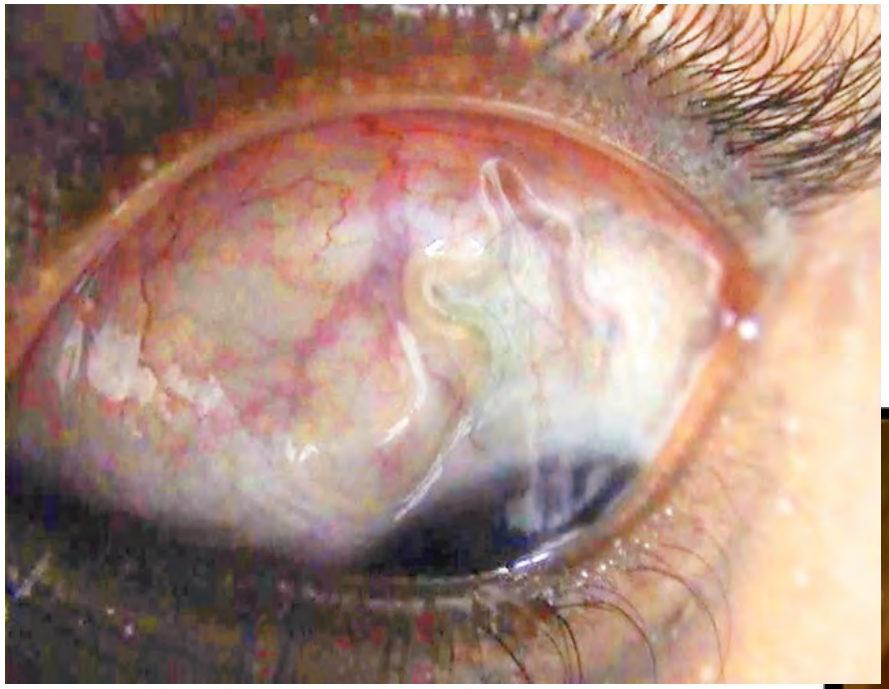
Loiasis - Clinical Manifestations

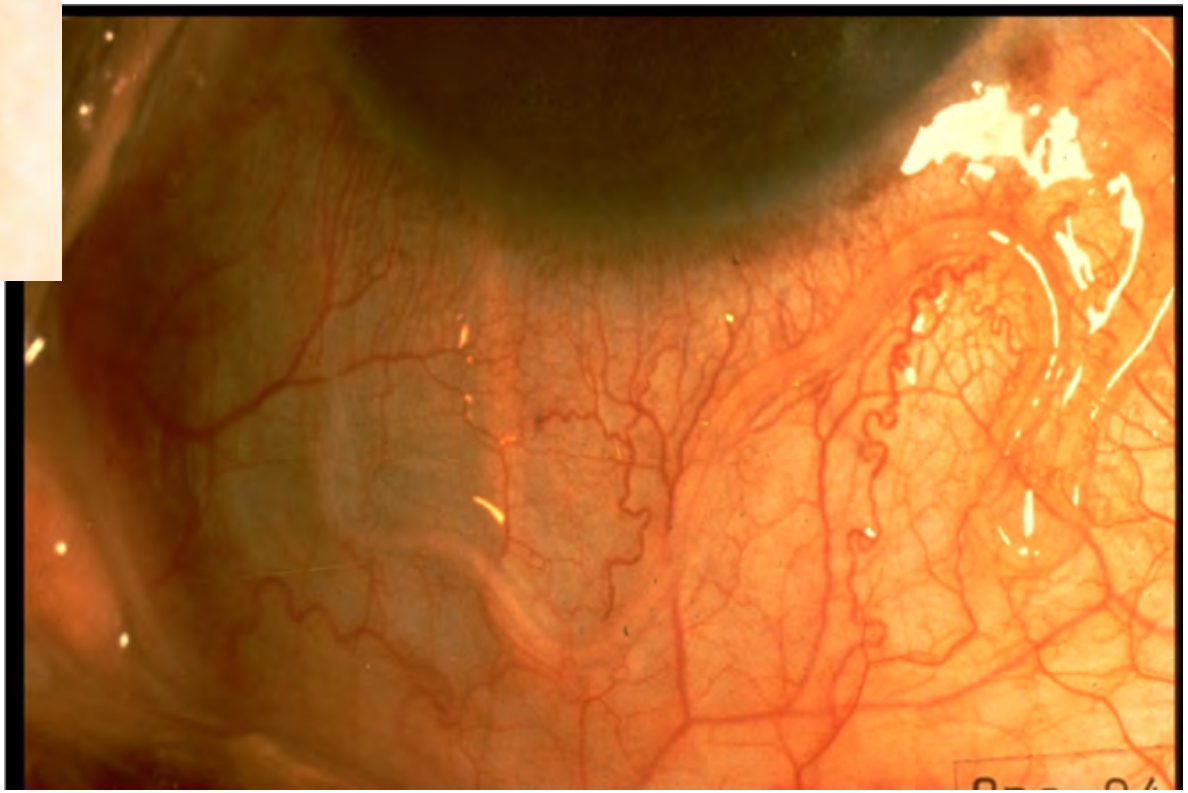
- Asymptomatic (subclinical)
- Non-specific
  - urticaria, pruritus, myalgias
- Calabar swellings
- Eyeworm
- Complications
  - Endomyocardial fibrosis, renal disease, encephalopathy, entrapment neuropathy

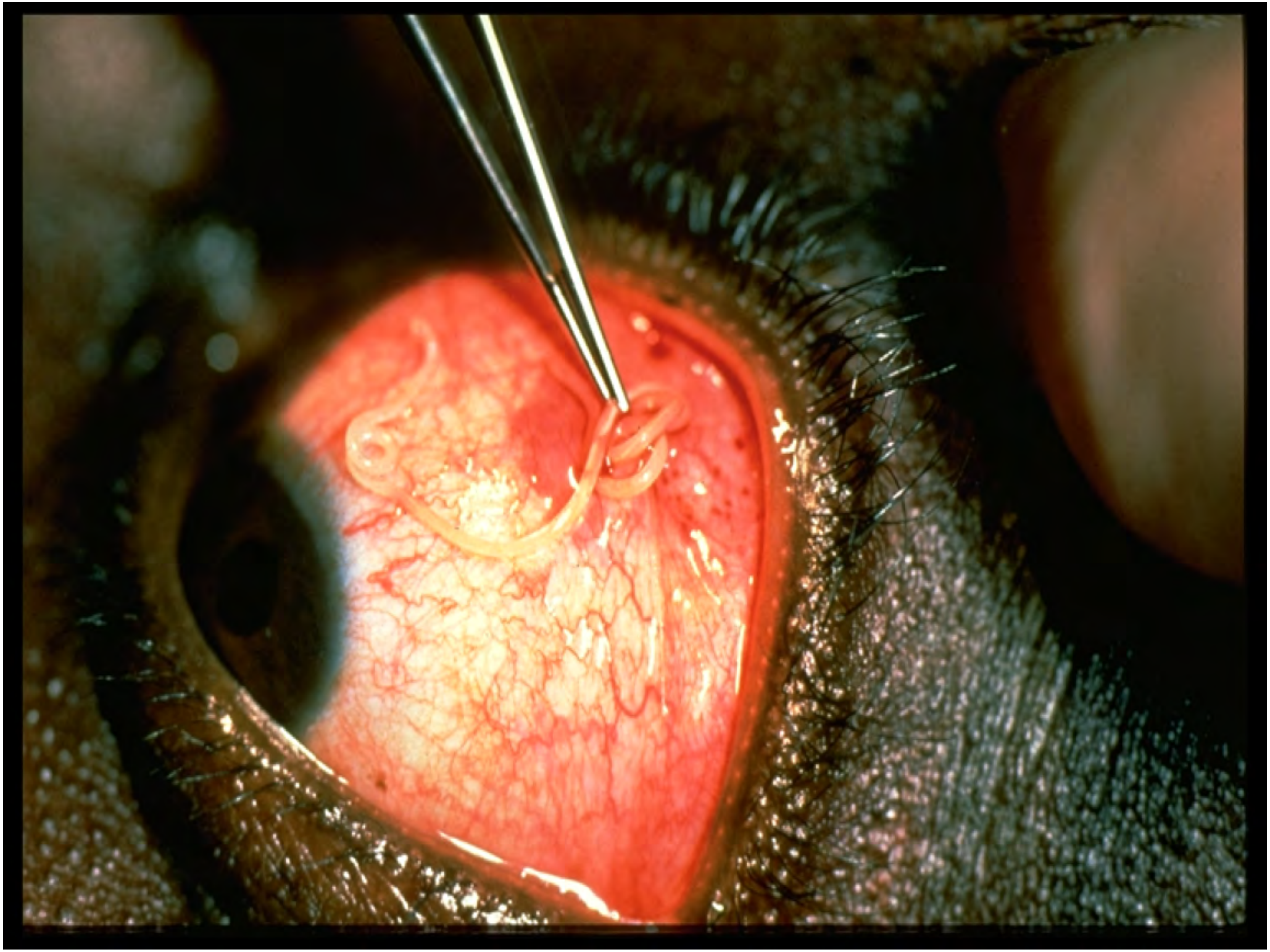
Loiasis – Calabar Swellings



Loiasis - Eyeworm







Clinical differences between endemic and non-endemic patients with loiasis

Manifestation	Expatriate N=42	Endemic (Benin) N=51
Calabar swelling	80%	16%
Eyeworm	10%	16%
Asymptomatic	16%	74%
Nonspecific		
Urticaria/myalgia/artrhralgia	54%	???
Complications		
Hematuria/proteinuria	21%	22%
Endomyocardial fibrosis	2%	???

Klion, A.D., A. Massougbodji, B.C. Sadeler, E.A. Ottesen, and T.B. Nutman. 1991 J Infect Dis 163:1318-1325

.

Clinical differences between endemic and non-endemic patients with loiasis

Manifestation	Expatriate N=144	Endemic N=37
Calabar swelling*	80%	15%
Eyeworm*	14%	62%
Asymptomatic (MF+)*	22%	74%
Nonspecific		
Urticaria*	19%	2%
Myalgia/arthralgia	22%	11%
Dermatitis	24%	16%
Lymphadenopathy*	11%	2%

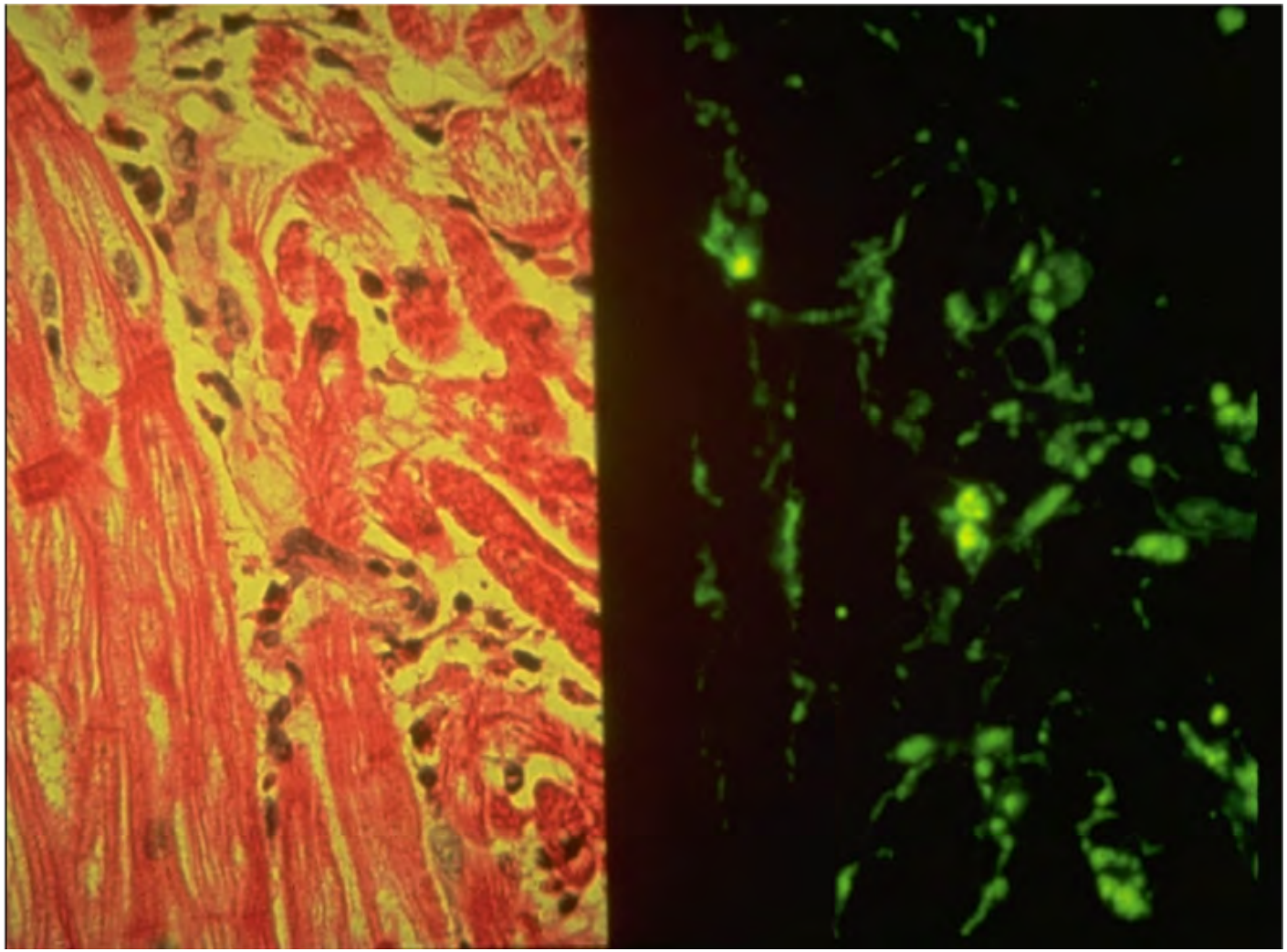
Herrick JA et al.Clin Infect Dis. 2015 ;60:684-693

Complications associated with *Loa loa* infection

Manifestation	Expatriate N=144	Endemic N=37
Hematuria/proteinuria	21%	22%
Endomyocardial fibrosis	0.4%	0%
Neuropsychiatric	0.4%	0%
Pulmonary	2%	3%

Herrick JA et al.Clin Infect Dis. 2015 ;60:684-693.

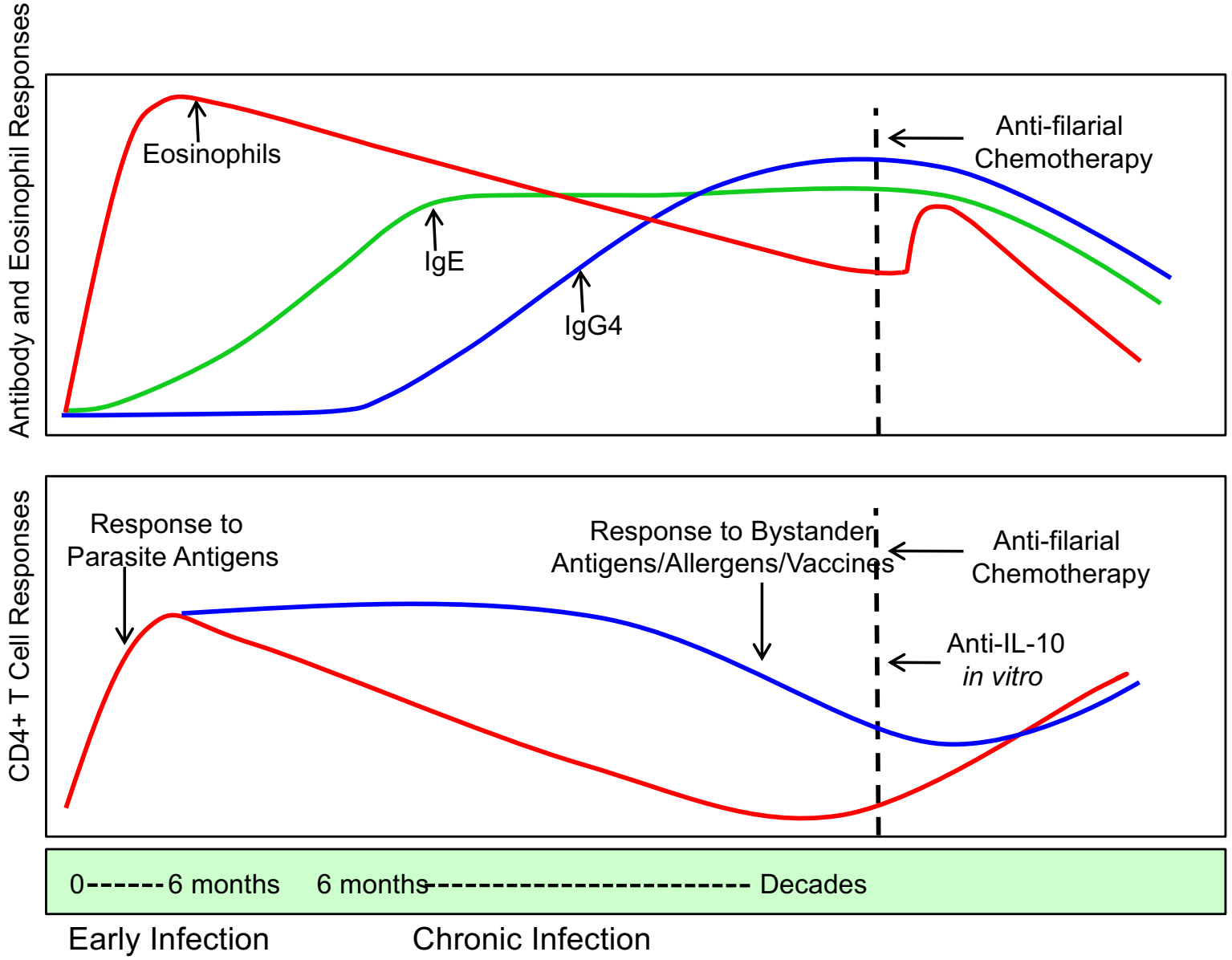
Eosinophilic endomyocardial fibrosis in a patient with loiasis

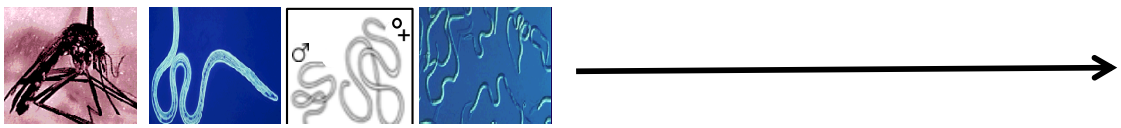


H and E

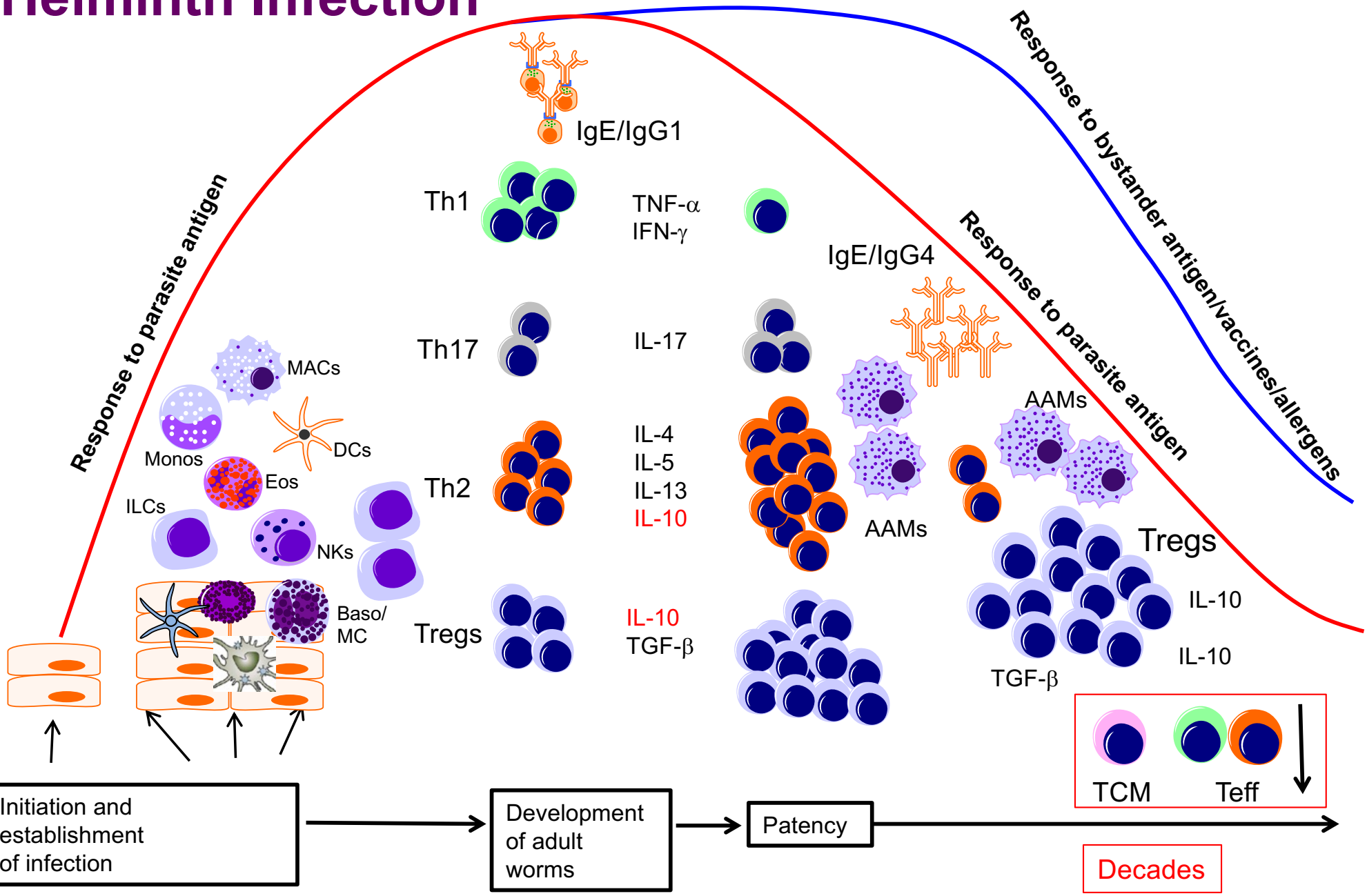
Anti-Eo-MBP

Modulation of Immune Response to Filarial Infection as a Function of Time





Immune Responses as a Function of Time in Human Helminth Infection



Parasite

Host

Uncontrolled response
Pro-inflammatory

Modulated response
Tolerant/suppressed

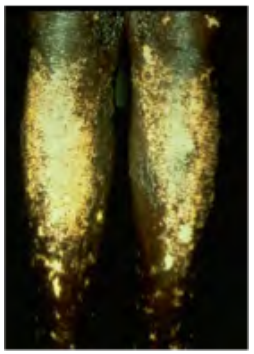
IL-10

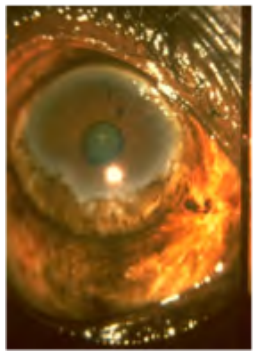
Immune-mediated pathology

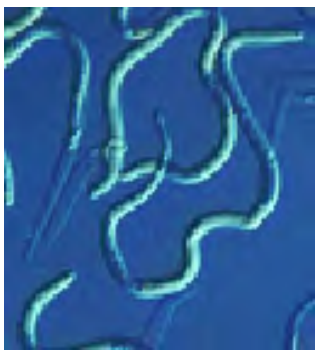
Patent subclinical infection

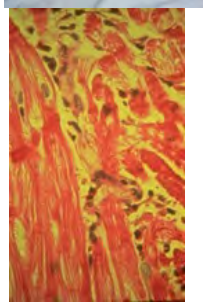
Lympahtic Filariasis

Onchocerciasis









Loiasis

Loiasis: treatment

- **Diethylcarbamazine (DEC)**
  - **treatment of choice**
  - **mechanism of action unknown**
  - **macro- and microfilaricidal**
  - **associated with severe side effects in patients with high levels of circulating microfilariae**
- **Ivermectin**
  - **microfilaricidal**
  - **also associated with severe side effects in patients with high microfilarial levels**

Loiasis: adjunct therapy

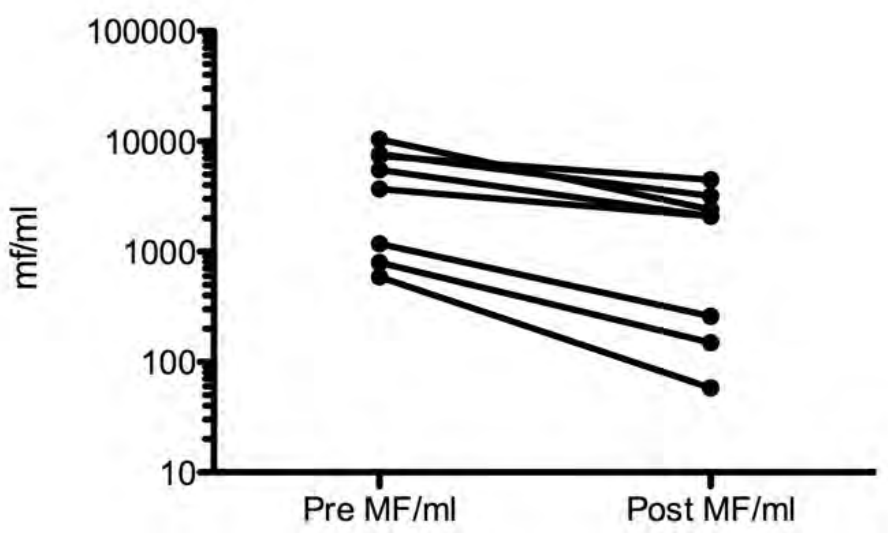
- **Corticosteroids**
  - decrease rate of microfilarial clearance
  - reduce severity of post-treatment reactions
  - DO NOT prevent severe CNS complications of treatment in patients with high microfilarial loads
- **Apheresis**
  - transient reduction of microfilarial load
  - ?decreased incidence of severe side effects

Filarapheresis

From 1990 - present

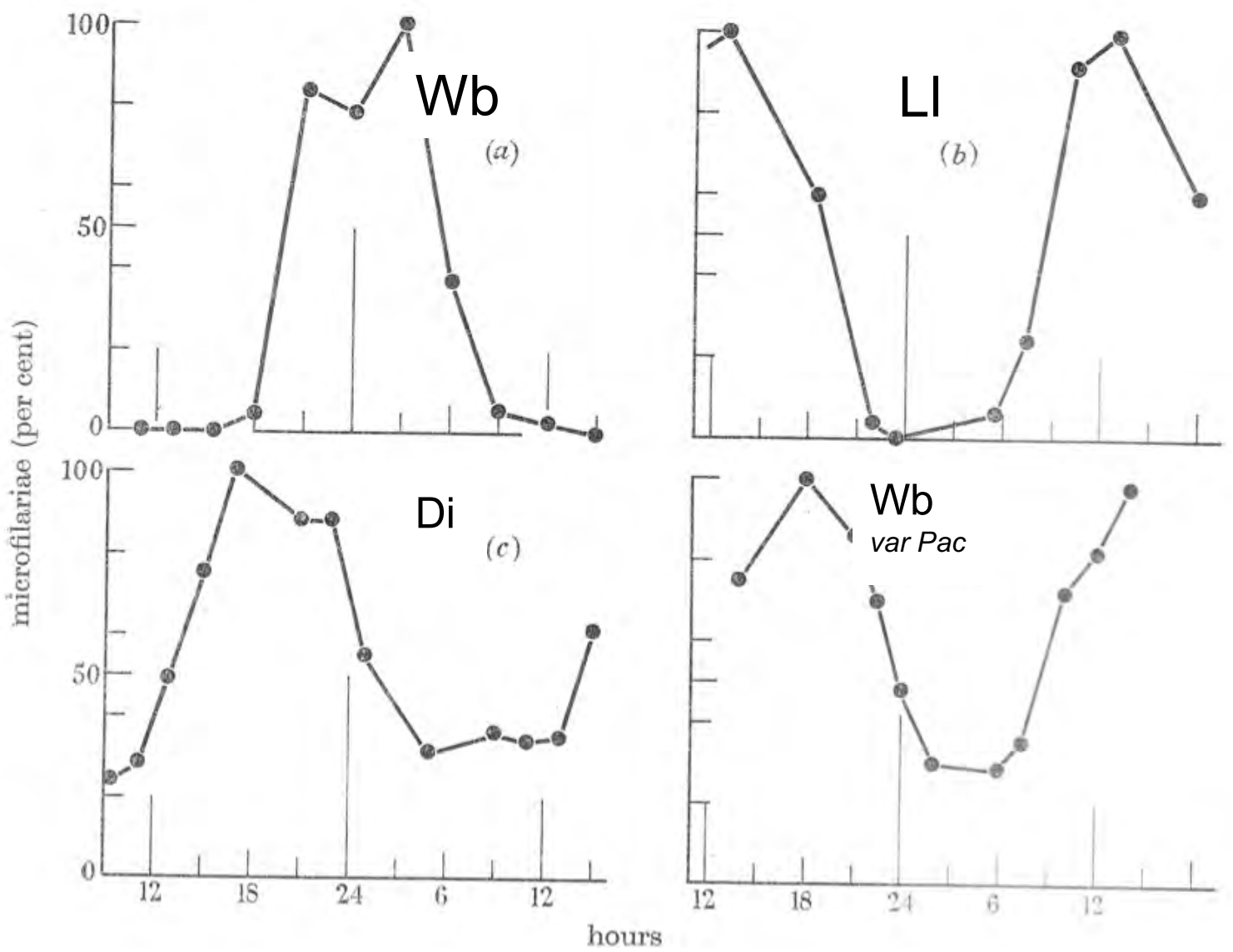
- **Numbers**
  - **46 heavily microfilaremic patients**
  - **68 procedures**
    - **Often on successive days**
- **Issues**
  - **Must be done at midday**

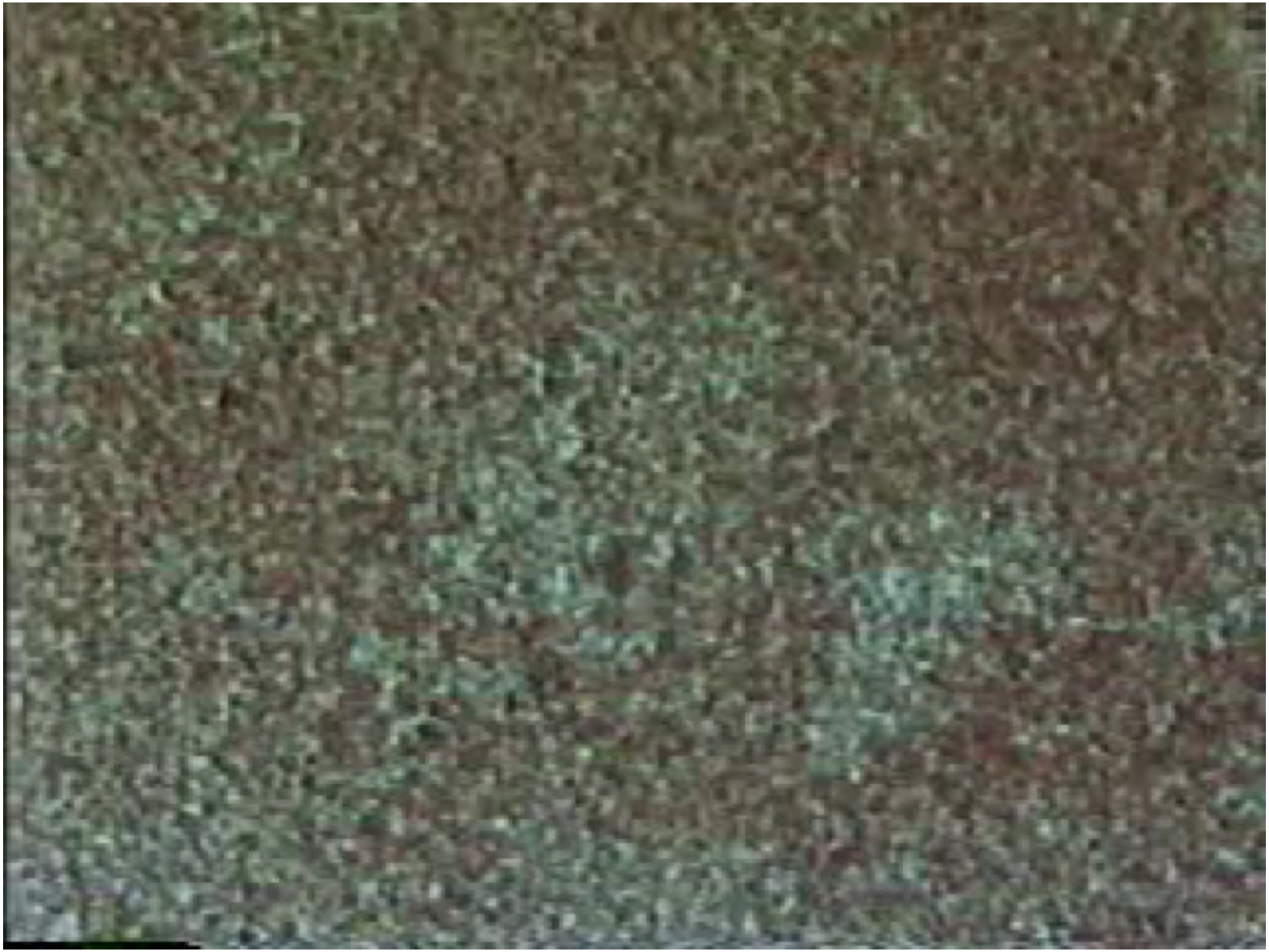
Efficiency of filarapheresis

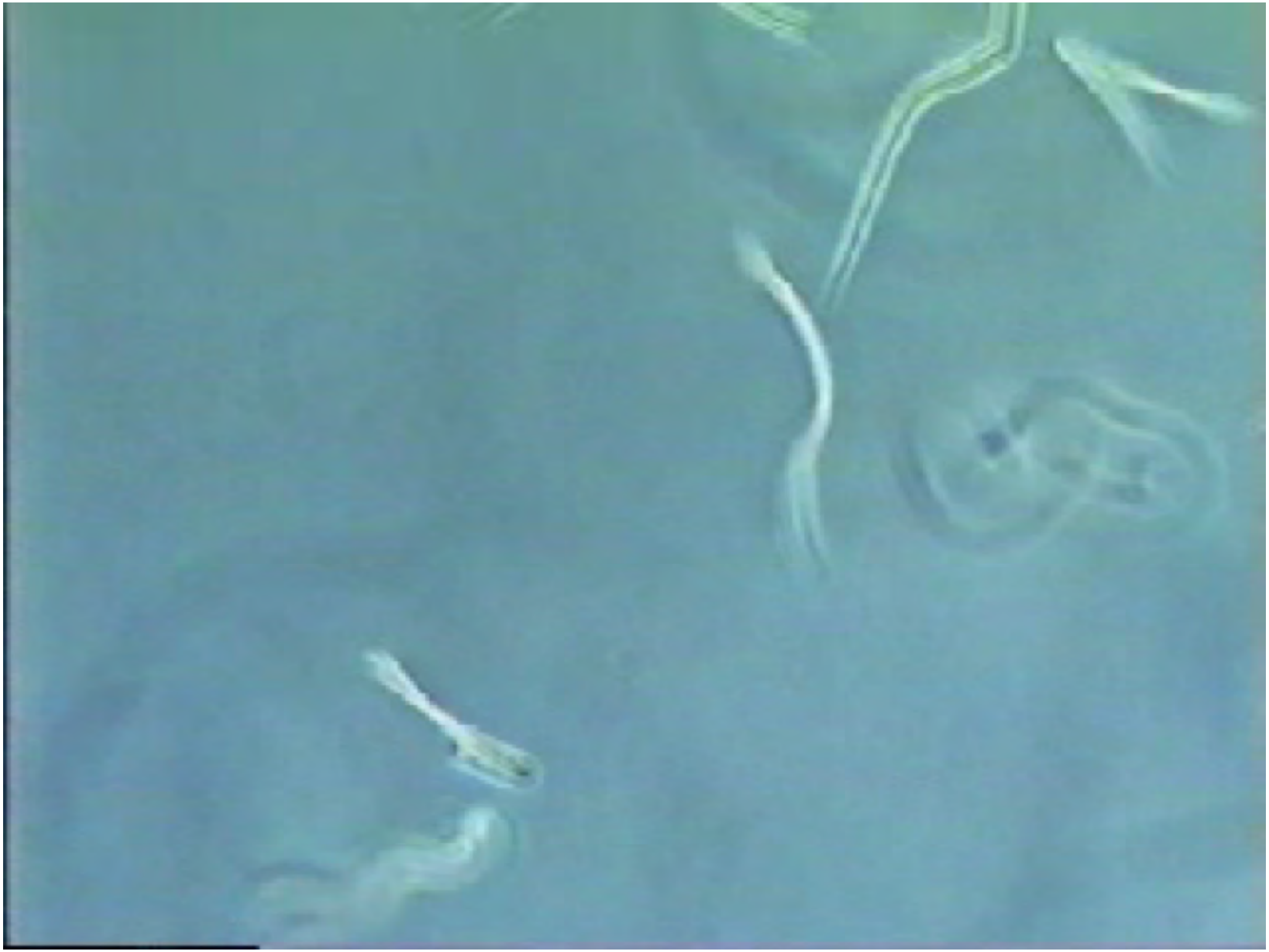


Average reduction 67%

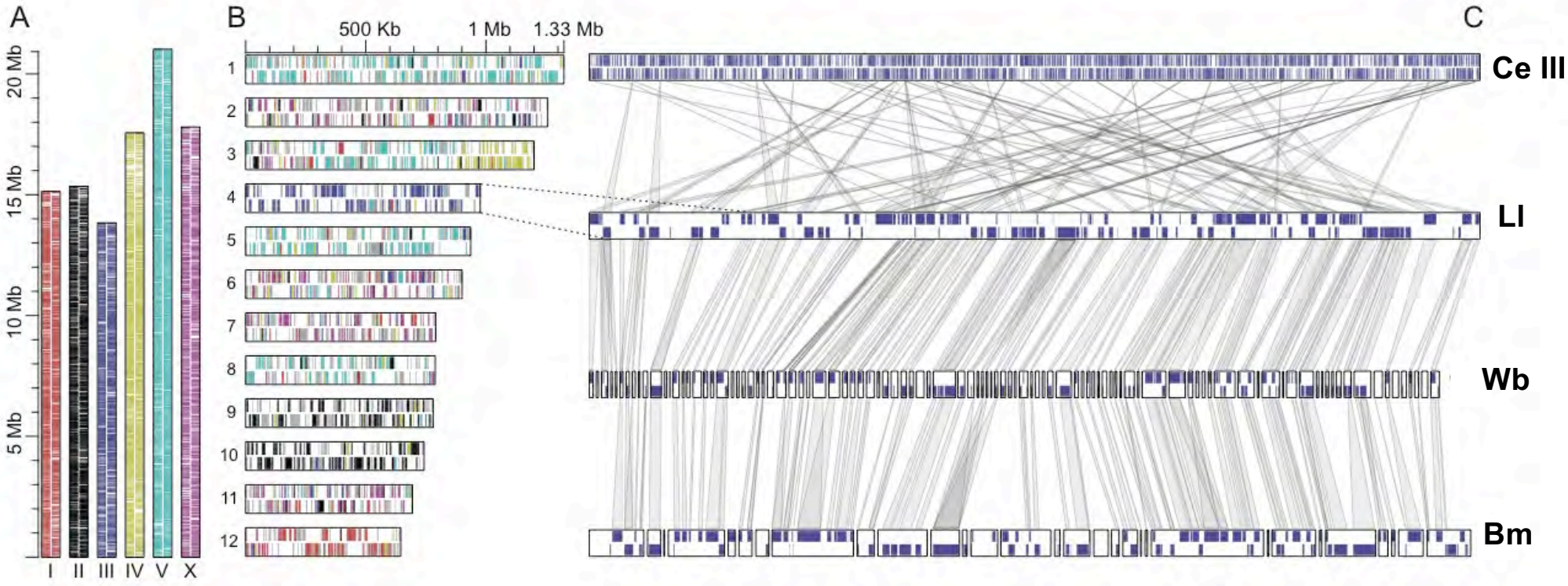
Periodicity of various microfilariae in blood







The *Loa loa* Genome



Chromosome Number

Genes mapped to largest scaffolds

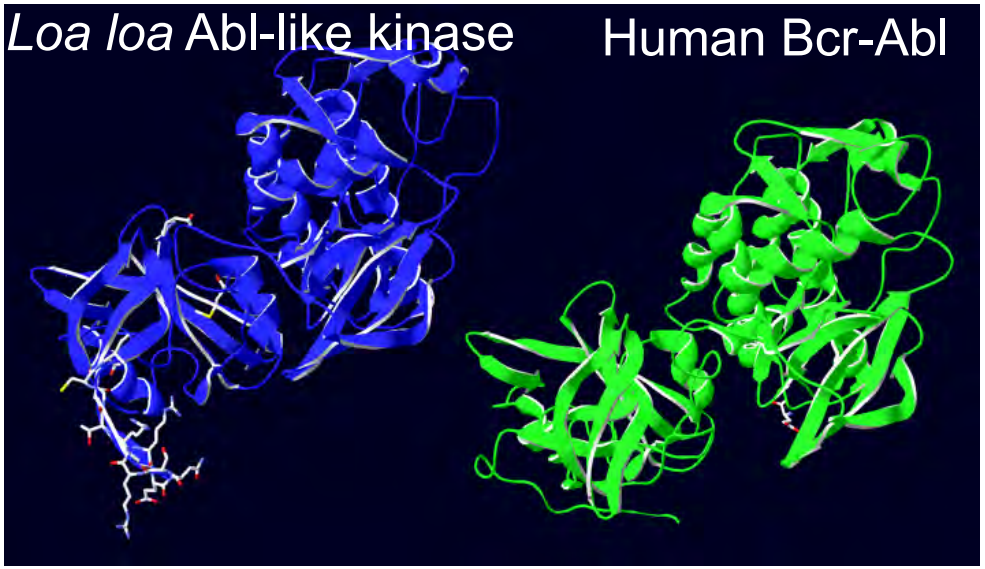
Extraordinary degree of synteny among the filariae

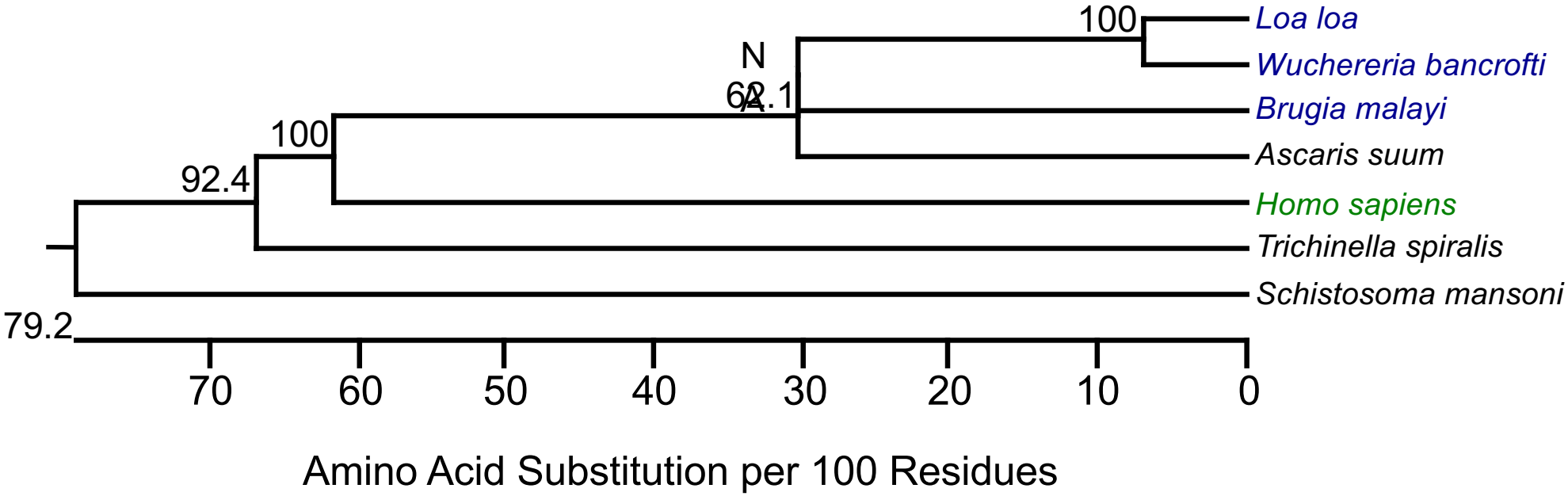
Desjardins et al *Nature Genetics* 2013

Worm kinases that are targets of FDA-approved drugs

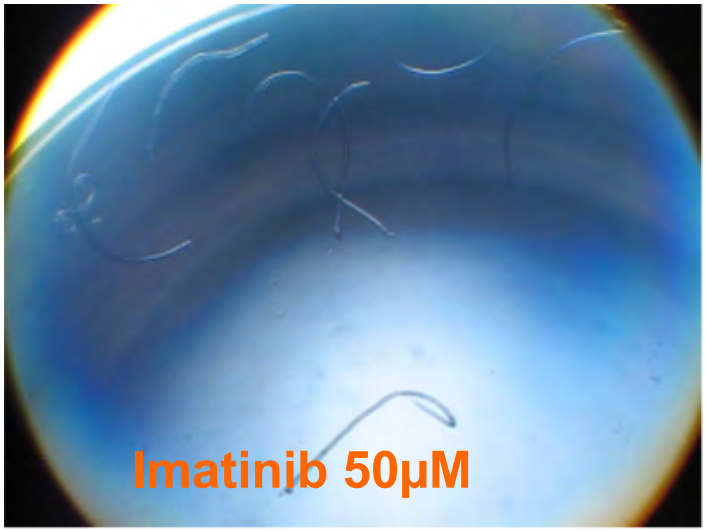
Classification	FPKM	L. loa	W. bancrofti	B. malayi	A. suum	P. pacifica	C. elegans	C.briggsae	M. hapla	T. spriralis	Approved drugs
AGC/DMPK/ROCK	58.18	1	1	2	1	0	1	1	1	1	Fasudil
ATYPICAL/PIKK/FRAP		2	1	3	1	2	1	1	1	2	Temsirolimus
TK/ABL	18.87	1	1	1	1	1	1	1	1	1	Imatinib, Nilotinib, Dasatinib
TK/EGFR	0.18	1	1	1	2	1	1	1	1	1	Gefitinib, Erlotinib, Lapatinib
TK/SRC	40.86	1	1	1	1	1	1	1	1	1	Dasatinib
TKL/RAF/RAF	27.55	1	1	2	1	1	1	1	1	1	Sonafenib

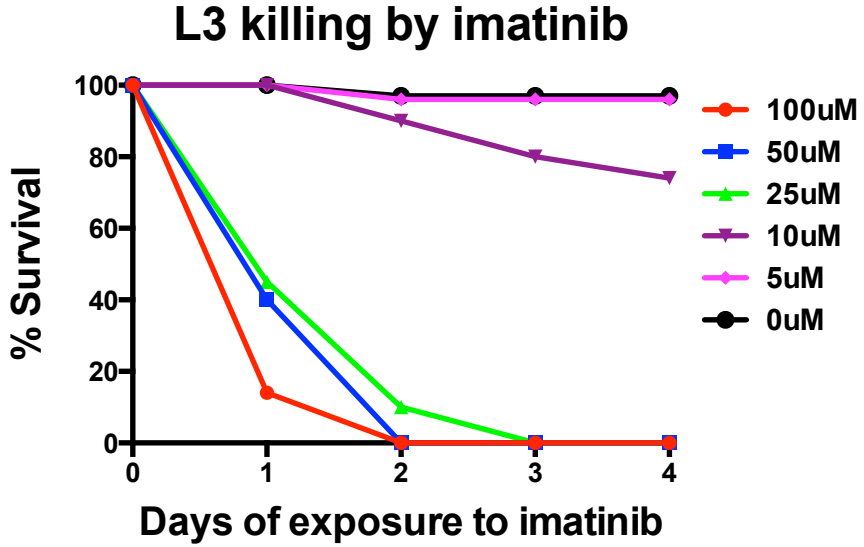
Structural similarity between the filarial abl-like kinase and the human Bcr-abl oncogene

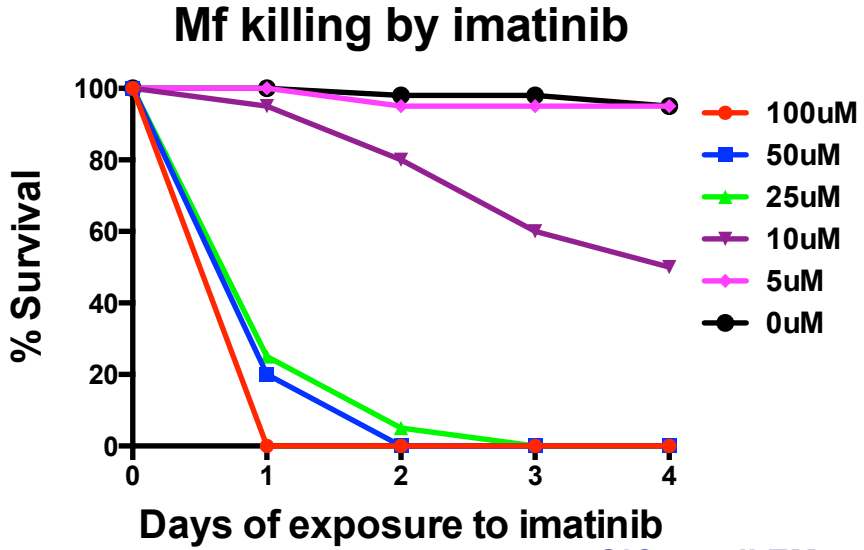




Repurposing imatinib for antifilarial chemotherapy

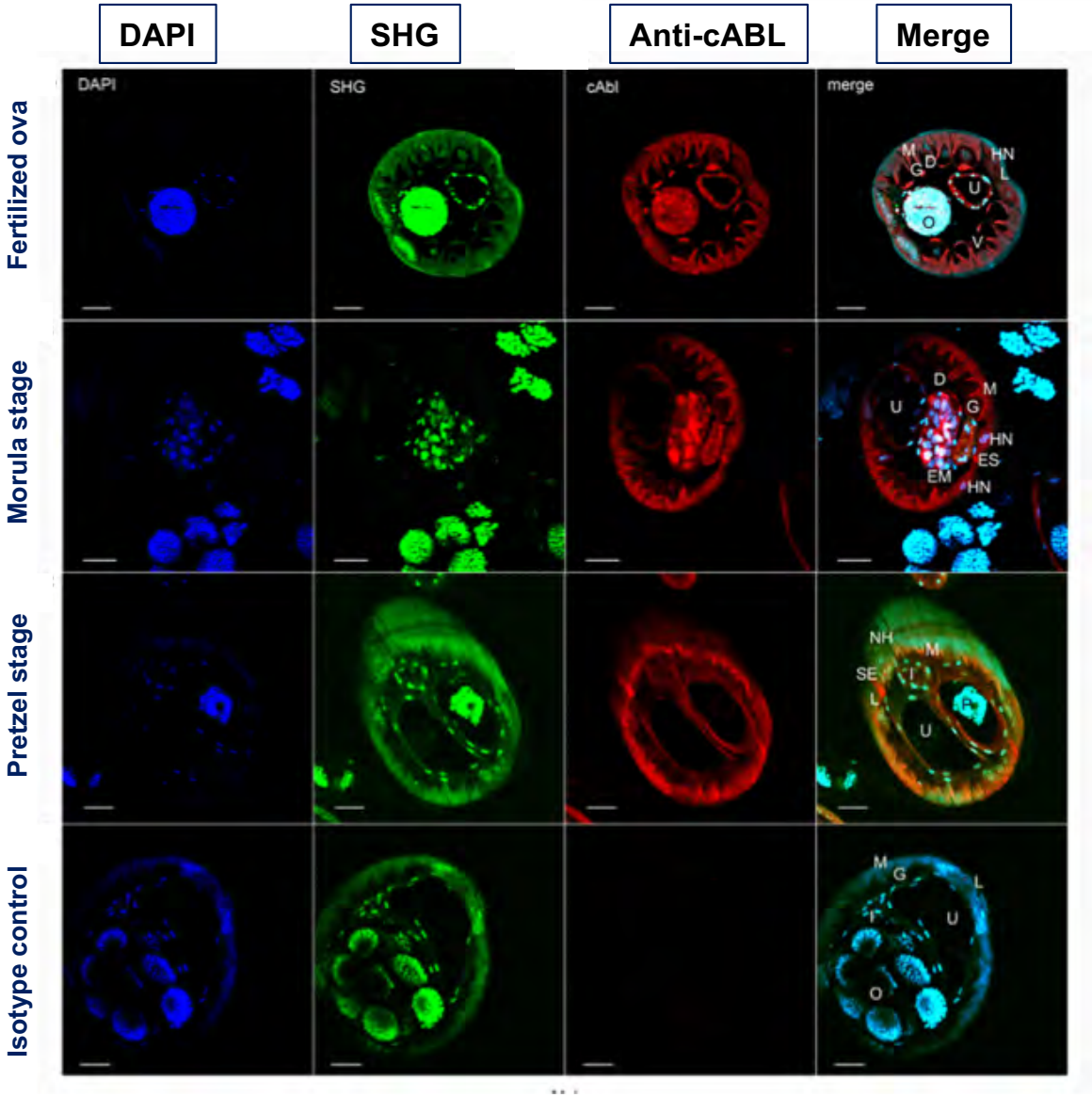






O'Connell EM et al, JID 2015

Filarial c-abl Localizes Most Strongly to the Female Reproductive Tract of the Filariae

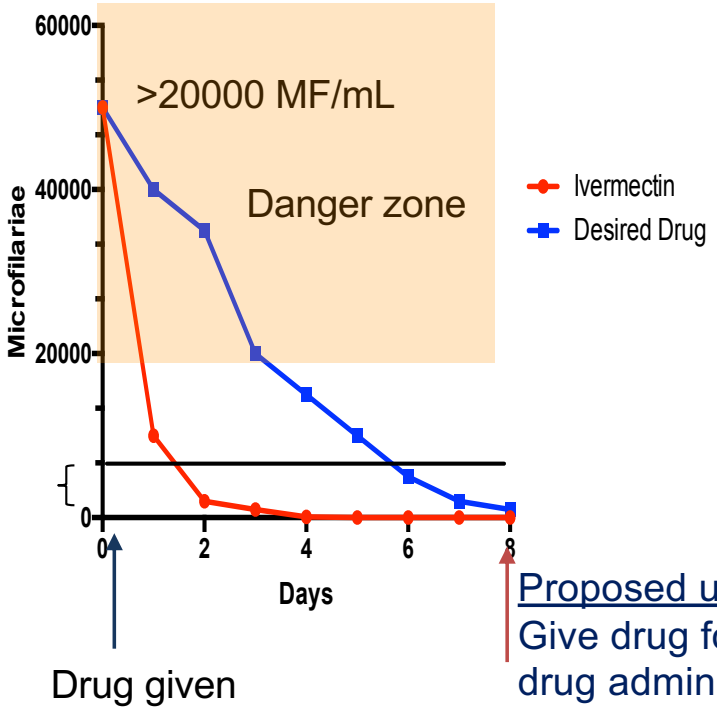


O'Connell EM, et al. PLoS NTD, 2017

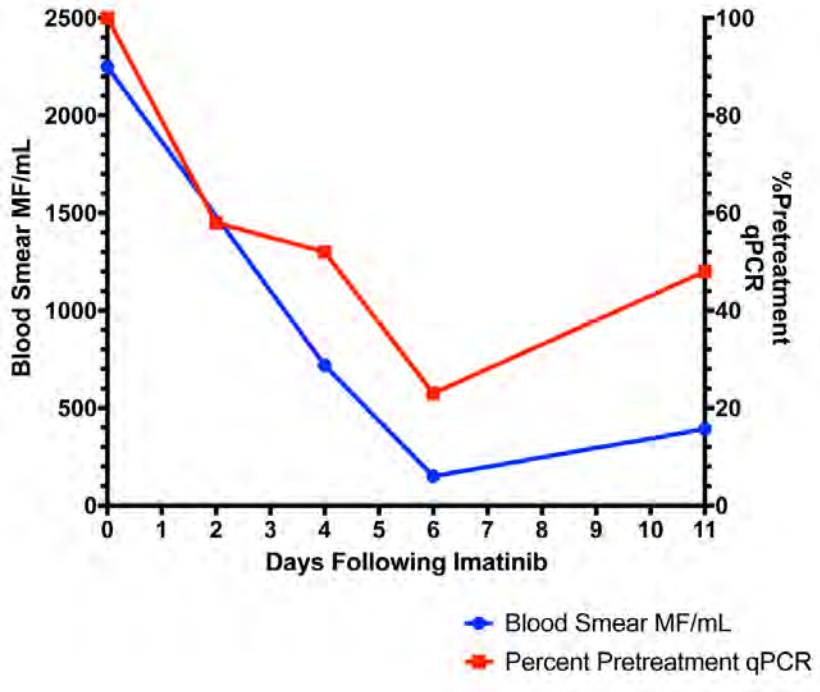
Clinical Protocol to Establish Efficacy and Safety of Single Dose Imatinib in *Loa loa* Microfilaremia

Randomized-controlled dose escalation trial of imatinib, evaluating the kinetics of *Loa loa* microfilarial (MF) response over 1 year in Cameroon

Severe adverse reactions (encephalopathy, death) to ivermectin is related to the *Loa loa* MF count and the rapidity with which it works



Proposed use:
Give drug for routine mass drug administration (MDA) during MF nadir to avoid severe reactions.




VOLVO
Turbo
OHIO
LOA LOA
3
HAMILTON
P
539 1151
OLVO

It Takes a ~~Village~~ Large Community

NIH
National Institute of Allergy and Infectious Diseases

New York Blood Center

CRFilMT
Centre de Recherche sur les Filarioses & Autres Maladies Tropicales

wellcome trust sanger institute

Erasmus MC
Universitair Medisch Centrum Rotterdam

Jefferson Medical College

PATH
A catalyst for global health

IRD
Institut de recherche pour le développement

MALARIA RESEARCH & TRAINING CENTER
BAMAKO MALI

College of VETERINARY MEDICINE
Michigan State University

REFORDE

McDONNELL GENOME INSTITUTE